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Proceeding Paper

Studying Anti-Alzheimer's Disease Theoretically Using Molecular Modeling Techniques †

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Abstract: Dementia is mainly caused by a chronic neurological disease called Alzheimer's disease (AD). Acetylcholinesterase (AChE) is an enzyme involved in the pathogenesis of neurodegenerative diseases. Its inhibition can improve the function of cholinergic neurons and modify the course of the disease. Researchers have discovered new opportunities for the development of innovative compounds using computational tools. The molecular modeling tools used in this study are aimed at finding new effective drugs to treat Alzheimer's disease (AD). Therefore, we conducted a study to evaluate the effects of various newly developed N-substituted 5-chloro-2(3H)-benzoxazolone derivatives on AchE. The study was a molecular docking study using MOE (Molecular Operating Environment) software. Molecular docking studies provide prospective evidence for identifying interactions between the active inhibitors and the AChE by predicting the manner of binding between the receptor and ligand, as well as their affinity. The analysis showed that molecules L1 and L10 have significant affinity with score energies of −8.741 and −8.492 kcal/mol, respectively. These chemicals are considered the most promising based on their docking score energies and hydrogen bond lengths. Therefore, the potential for further investigation of these compounds to develop drug compounds for the treatment of neurodegenerative diseases has been demonstrated.

Keywords: Alzheimer's disease; AChE; Inhibition; Molecular docking; N-substituted 5-chloro-2(3H)-benzoxazolone derivatives

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1. Introduction

Alzheimer's disease (AD) is the most common single cause of dementia in aging societies [1]. It causes a slowly progressive, irreversible destruction of mental performance. The disease is characterized by a gradual loss of function. Short-term and long-term memory are impaired, while language skills, attention and concentration are often impaired. Restlessness, personality changes, delusions and hallucinations occur [2].

Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by tau pathology and accumulations of neurofibrillary tangles (NFTs) along with amyloid-beta (Aβ). Acetylcholinesterase inhibitors (AChEI) inhibit this aggregation by binding to AChE.

Although acetylcholinesterase inhibitors are not a cure for the disease, these drugs can slow the progression of mental decline and alleviate neuropsychiatric symptoms, and therefore represent a reasonable therapeutic approach for the treatment of AD.

Molecular docking is a computational drug design approach widely employed in lead discovery because it reduces both the time and cost of the discovery process. The docking system is based on scoring functions that indicate the binding energy of the ligands when bound to their receptors and different types ofinteractions present between certain amino acids of the protein studied and that of ligands.

2. Materials and Methods

Eleven compounds belonging to N-substituted 5-chloro-2(3H)-benzoxazolone derivatives were studied by molecular docking, were tested with, MOE [3], and othersoftware programs were used to find optimal high-affinity compounds.

3. Results and Discussion

The molecular docking results in this study are evaluated based on three key parameters: energy score (S-score, kcal/mol), interaction types and distances, and the RMSD (Root Mean Square Deviation) value.

Table 1. Docking score energy, RMSD values and interactions of studied compounds with active site residues of AChE (PDB ID: 4EY7).

Componds	S-Score (kcal/mol)	RMSD (Å)	Bonds Between Atoms of Compounds and Active Site Residues				
			Atom of Compound	Involved Receptor Atoms	Involved Receptor Residues	Type of Interaction Bond	Distance (Å)
ACHE							
L1	−8.741	1.022	H1	O	HOH954	Water Hydrogen Bond; Conventional Hydrogen Bond	2.65
			H	O	HOH931	Water Hydrogen Bond; Carbon Hydrogen Bond	2.01
			HA	O	PHE338	Carbon Hydrogen Bond	2.20
L10	−8.492	1.752	H1	O	HOH731	Water Hydrogen Bond; Conventional Hydrogen Bond	2.82
			H1	O	HOH954	Water Hydrogen Bond; Conventional Hydrogen Bond	2.48
			H	O	HOH955	Water Hydrogen Bond; Carbon Hydrogen Bond	2.61
			H	O	HOH931	Water Hydrogen Bond; Carbon Hydrogen Bond	2.12
			H	O	PHE295	Conventional Hydrogen Bond	2.53
			HA	O	PHE295	Carbon Hydrogen Bond	2.65
			HD2	CL	HIS447	Carbon Hydrogen Bond	2.56
			H	OD2	ASP74	Carbon Hydrogen Bond	3.09
			H	OH	TYR124	Carbon Hydrogen Bond	2.75
Donepezil	**−11.247**	0.408	N-14	O	HOH931	H-donor	2.79
			C-15	6-ring	TYR337	H-Pi	4.11
			6-ring	6-ring	TRP286	Pi-Pi	3.73

According to the results of molecular docking studies (Figure 1), the most stable complexes were formed when molecules L1 and L10 were incorporated into AChE (PDB ID: 4EY7). The complexes formed by compounds 1 and 10 had low energy values (−8.741 and −8.492 kcal/mol, respectively) and good RMSD values of 1.022 (Å) and 1.752 (Å), respectively, which were very close to the natural ligand donepezil (−11.247 kcal/mol).

It is also obvious that compound L1 forms three strong hydrogen bonds with the active site residues of the AChE target.

On the other hand, L10 forms nine strong hydrogen bonds with the active site residues. This means that they are also considered excellent candidates for further studies.

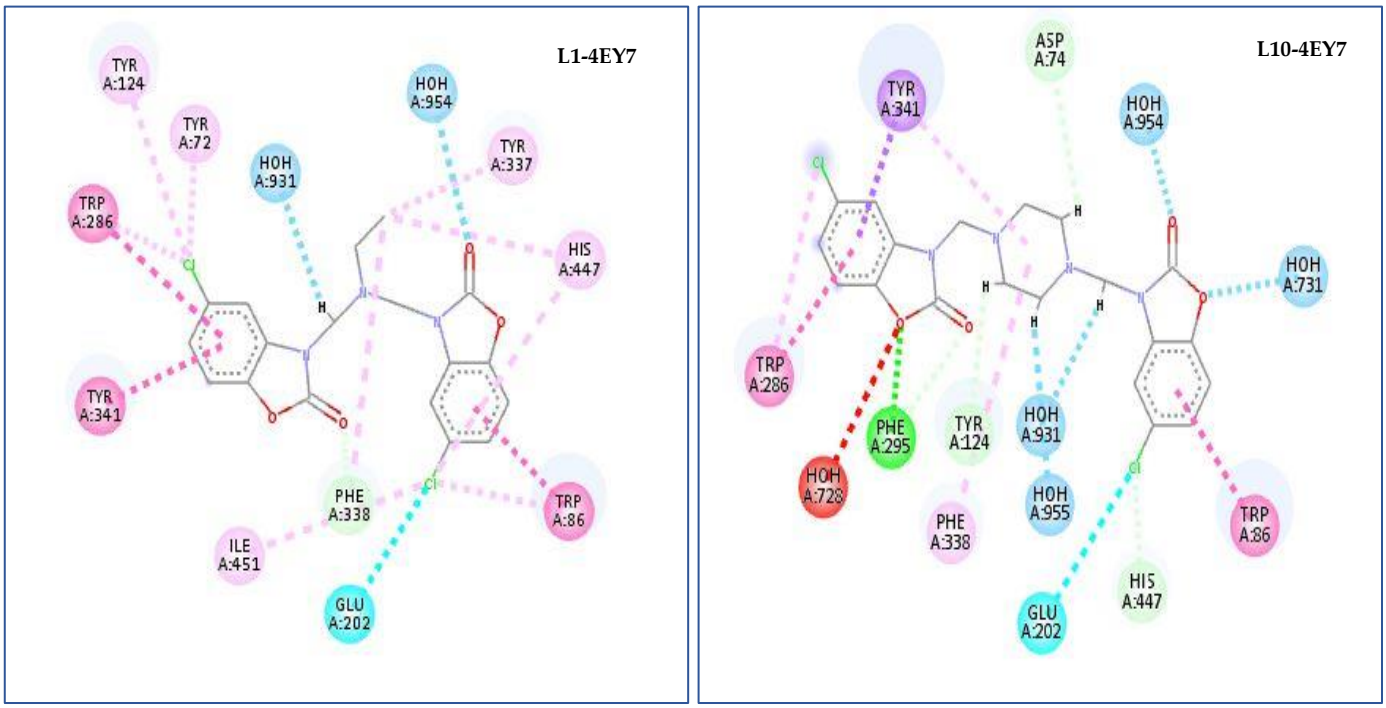

Figure 1. 2D representation of the best pose interactions of complexes: L1-4EY7, L10 -4EY7using molecular docking simulation.

4. Conclusions

Molecular docking simulation results showed that compounds 1 and 10 have high binding affinity to the target, as evidenced by low energy values and various interactions with active site residues. This was confirmed by the root mean square deviation (RMSD) values of most of the complexes formed being no more than 2 Å, suggesting that they could serve as prime drug candidates for the treatment or inhibition of Alzheimer's disease (AD).

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